PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70) 14

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
SCB/53202/001		
International application No. PCT/EP00/04918	International filing date *(day/month/year)* 26/05/2000	Priority date *(day/month/year)* 29/06/1999
International Patent Classification (IPC) or national classification and IPC C12N15/11		
Applicant JANSSEN PHARMACEUTICA N.V. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
18/12/2000	19.07.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Bretherick, J Telephone No. +49 89 2399 8415

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/04918

I. Basis f the r port

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-58 as originally filed

Claims, No.:

1-46 as originally filed

Drawings, sheets:

1/5-5/5 as originally filed

Sequence listing part of the description, pages:

55-58, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☒ furnished subsequently to this Authority in computer readable form.
- ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 24,25,31-35.

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 24,25,31-35.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☐ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☒ not complied with for the following reasons:
see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☐ all parts.

☒ the parts relating to claims Nos. 1-23,26-30,36-46.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	6,14,15,18-23,28,30,36,37,40-42,44
	No:	Claims	1-5,7-13,16,17,26,27,29,38,39,43,45,46
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-23,26-30,36-46
Industrial applicability (IA)	Yes:	Claims	1-23,26-30,36-46
	No:	Claims	

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

1. **Regarding Part V, Art. 33 PCT:**

a. Only the subject-matter of claims 3, 6,14, 21 and 46 and corresponding dependent claim embodiments are entitled to the priority rights of priority application 9915200.1 The remaining claimed subject-matter does not enjoy priority since it is not **directly and unambiguously** disclosed therein. Moreover, subject-matter pertaining to Rat sequences in the priority document does not render subject-matter in the application defined as mammalian human or mouse entitled to the priority right without there being a literal disclosure thereof.

For subject-matter not enjoying priority, WO9950298 (published 7/10/1999), WO0005373 (published 03/02/2000) are art under Art. 33 PCT. This also applies or those additional non-patent documents cited in the International Search report as "P,X".

For subject-matter enjoying priority, WO9950298 (published 7/10/1999) and WO0005373 (published 03/02/2000), are cited under **R. 70.10 PCT (Re. Part VI).**

b. **D1** DATABASE EMBL [Online] EMBL; ID AF155960, AC AF155960, 28 July 1999 (1999-07-28) GUNN T M ET AL.: 'Mus musculus recombination breakpoint containing region' XP002152927 cited in the application discloses the coding sequence of mouse GFRα-4. This has 99.6% identity with SEQ ID NO, 1 (2) in a 280 (290) nt overlap. **D2**, DATABASE EMBL [Online] EMBL; ID AW528607, AC AW528607, 8 March 2000 (2000-03-08) SOARES M B: 'UI-R-BO1-ajr-c-09-0-UI.sr UI-R-BO1 Rattus norvegicus cDNA clone, UI-R-BO1-ajr-c-09-0-UI 3', mRNA sequence' XP002153002 discloses the rat equivalent. **D3,** DATABASE EMBL [Online] EMBL; ID MMU276872, AC AJ276872, 1 May 2000 (2000-05-01) AIRAKSINEN M S: 'Mus musculus mRNA for GDNF family receptor alpha 4, putative secreted isoform (Gfra4 gene) also discloses a mouse equivalent coding sequence.

The subject-matter of claims 1-5, 7 and 45 is therefore not new under Art. 33(1)(2) PCT. Note that the above art discloses equivalents to the sequences defined in claim 3.

c. The chicken GFRα-4 sequence disclosed in **D4** :THOMPSON J ET AL.: 'GFRalpha-4, a new GDNF family receptor' MOLECULAR AND CELLULAR NEUROSCIENCE, vol. 11, no. 3, June 1998 (1998-06), pages 117-126, XP000960388 and cited in the application also falls under the claimed scope. According to **D5,** ENOKIDO Y ET AL.: 'GFRalpha-4 and the tyrosine kinase Ret form a receptor complex for persephin' CURREN BIOLOGY, vol. 8, no. 18, 10 September 1998 (1998-09-10), pages 1019-1022, XP000960386 cited in the application this receptor has persephin as ligand. Transient expression of chicken GFRα-4 in cultured and human embryonic 293 kidney cells and in neuronal cells, enabled the testing of the interaction of the receptor and various potential ligands. In neuronal cells, the coexpression of the GFRα-4 receptor and RET tyrosine kinase enabled in increase survival upon exposure to persephin.

The subject-matter of claims 8-13, 16 and 17, as well as methods claims 26, 27, 29, 38, 39, 43, 45 and 46 is therefore also not new.

d. **D6**, WO 97 33912 A (GENENTECH INC ;RYAN ANNE M (US); KLEIN ROBERT D (US); MOORE MARK W) 18 September 1997 (1997-09-18) discloses the expression of GFRα (here called GDNFR). The type is not indicated. Antibodies thereto, probes based upon subunits thereof are also disclosed, as well as assays which measure the degree of tyrosine phosphorylation occurring in RET in a variety of cells coexpressing GFRα. Transgenic mice expressing GFRα are also disclosed. Methods of therapy using antibodies and antisense to GFRα are also discussed.

The difference between the currently claimed subject-matter and the above lies merely in the sequence. The technical problem solved by the current claim set is thus the provision of alternative GFRα types. This has already been solved in D4 and D5, the latter showing that the ligand persephin reacts with the chicken GFRα-4.

D7, WO 99 14235 A (MILBRANDT JEFFREY D ;DESAUVAGE FRED (US); KLEIN ROBERT (US); UNIV) 25 March 1999 (1999-03-25), discloses the ligand to the currently claimed receptor, as well as therapies involving its use.

From the teachings of D4, D5 or D6, the skilled person might expect to find alternative forms of GFRα expressed in mammals using techniques based on the art. As such the claimed subject-matter cannot be considered to involve an inventive step, even when taking the individual sequence characteristics into account.

2. Regarding Part IV, unity of invention, R. 13.1 PCT:

The International Examining Authority shares the opinion of the International Searching Authority that the subject-matter of the application lacks unity within the meaning of R. 13.1 PCT.

The mouse equivalent GDNF family receptor (GFRα-4) has been disclosed in Gunn et al. (1999) Nature, Vol. 396, pp. 152-156, (see page 153, RH. column, lines 11 et seq., figure 2d, GFRA-4). The sequence has also been disclosed in the P,X document **D1,** cited above. Since the priority of the application is not uniformly valid, and for the above given reasons lacks novelty, the common concept of mammalian DGNF family receptor - encoding DNA is therefore not novel.

The claims provide assorted solutions addressing the known problem of provision of further GDNF receptor family members and encoding DNA and associated uses thereof and/or therefore.

The International Searching Authority considered it unnecessary to demand a further search fee. The same applies with respect to the examination fee. However, it should be noted that the parts of claims relating to DNA of mammalian, human, rat and mouse origin respectively, provide different solutions to the same problem, which do not have any new common feature(s). They therefore lack unity of invention under R. 13.1 PCT.

3. **Regarding clarity, (Art. 6 PCT: Part VIII):**

Certain claims contain neither direct nor indirect reference to stuctural features. These are not clear **per s** and should be corrected making reference to the available sequence listings.